Current biologics for severe asthma and response assessment

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Disclosures

Michael Wechsler, M.D., MMSc.

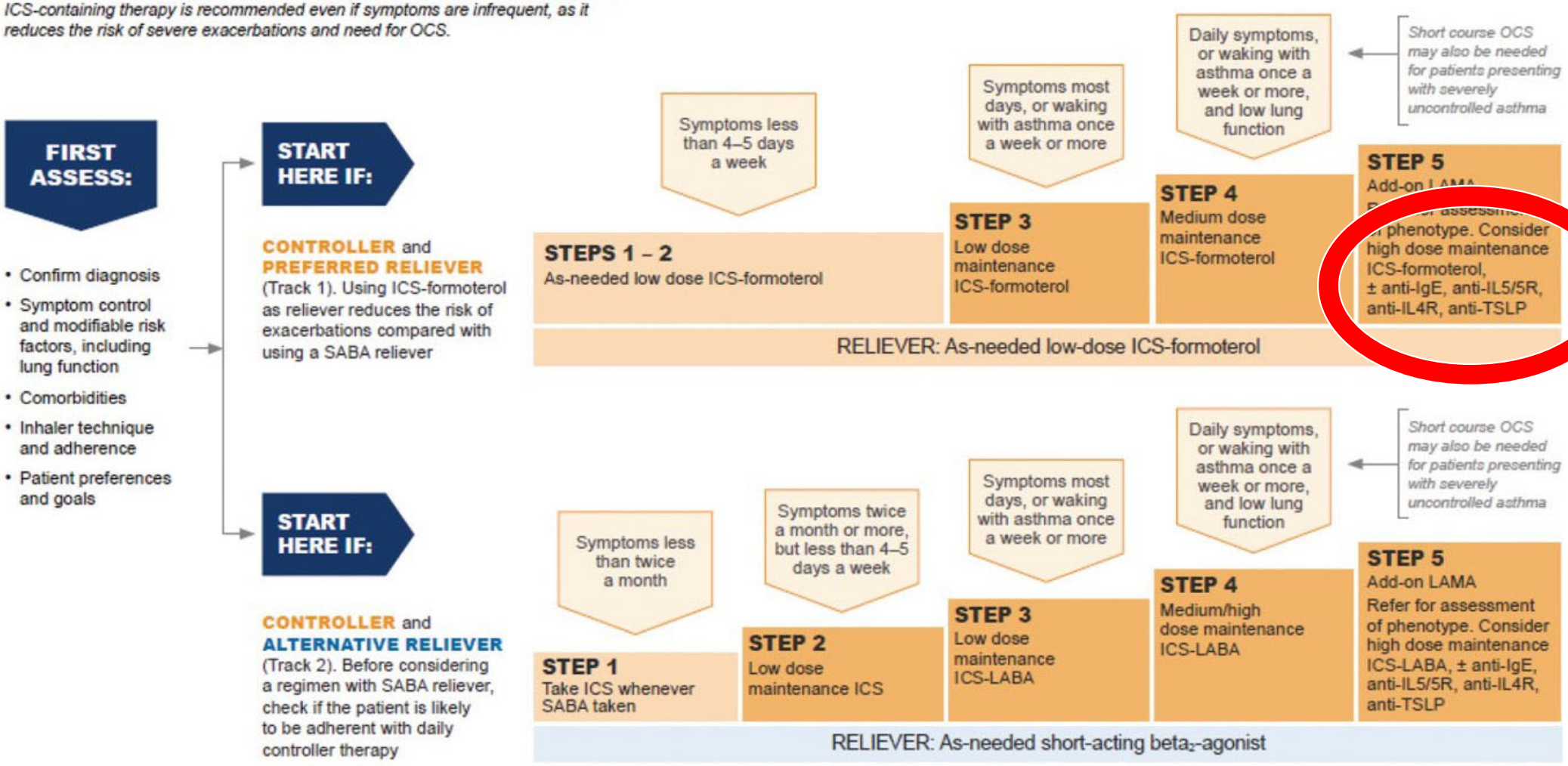
- Consultant/Honoraria: AstraZeneca, Amgen, Glaxosmithkline, Sanofi, Genzyme, Regeneron, Boehringer Ingelheim, Novartis, genentech, Pulmatrix, Teva, Equillium, cytoreason , Restorbio, Cohero Health, cerecor, incyte, sound biologics, kinaset

GINA Guidelines

STARTING TREATMENT

in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller. ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.



ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist. See Box 3-6, p.63 for low, medium and high ICS doses for adults and adolescents.

When do I consider biologics for severe asthma?

- Poor asthma control
  - Asthma symptoms despite ICS/LABA
  - Interference with daily activity
  - Interference with sleep
  - Chronic OCS use
  - At least 2 exacerbations in prior year

What about low FEV1?

- Only if accompanied by symptoms

Before starting biologics

- Confirm asthma diagnosis
- Maximize therapy- usually ICS/LABA/LAMA
- Confirm adherence/inhaler technique
- Address complicating comorbidities
  - Sinus disease
  - Reflux
  - Aspiration
  - OSA

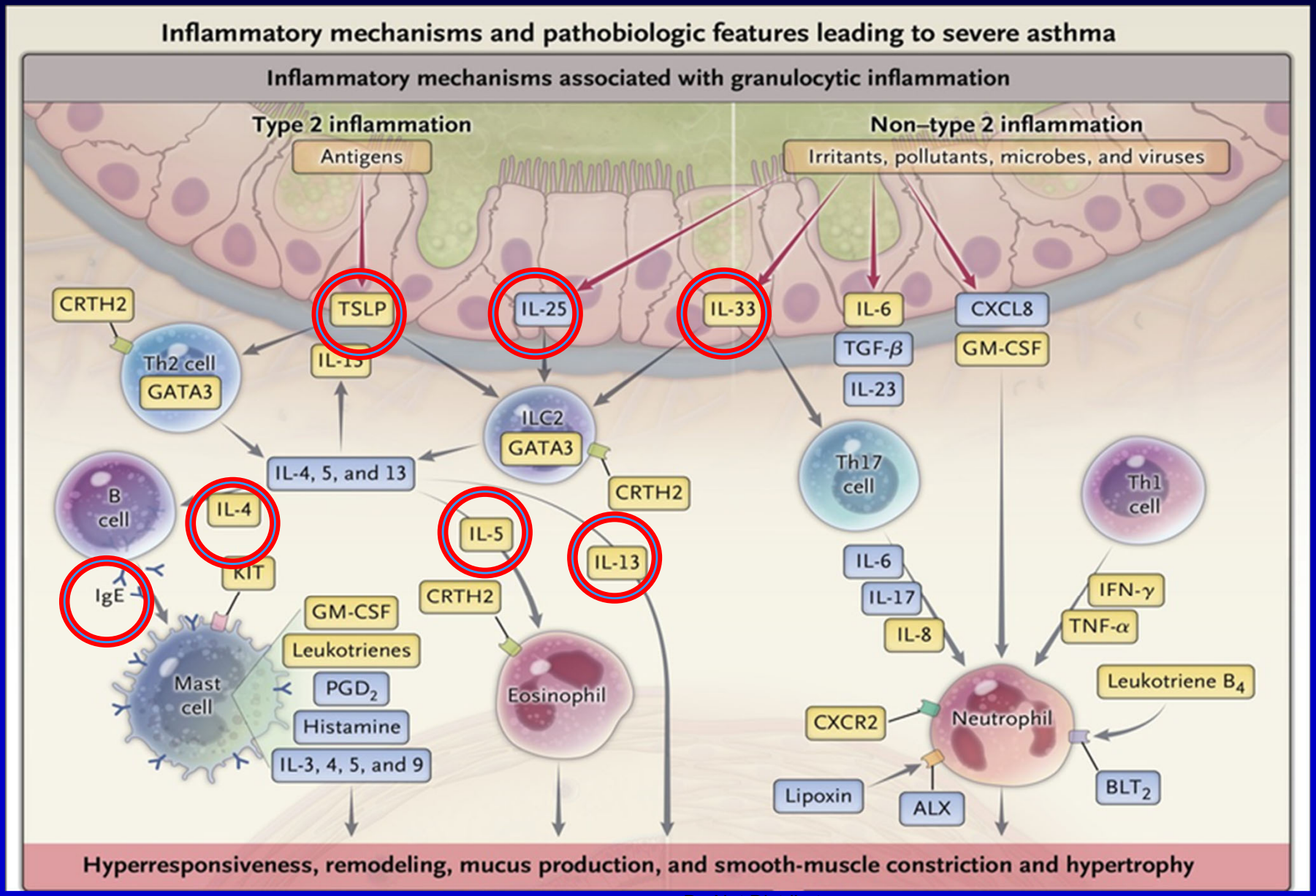
If….

- Asthma confirmed
- Therapy maximized
- Adherence/technique optimized
- Comorbidities addressed

… then -and only- then will I consider biologics

What are my biologic options?

There are Many Potential Targets in Severe Asthma



From Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. Drazen JM, ed. *N Engl J Med*. 377(10):965-976. Copyright© 2017 Massachusetts Medical Society. Reprinted with

Current Asthma Biologics

- Anti IgE- Omalizumab
- Anti IL5: mepolizumab, reslizumab, benralizumab
- Anti IL4- R alpha/Anti IL13: dupilumab
- Anti TSLP: Tezepelumab

What can we achieve with biologics?

- Reduced exacerbations
- Reduced steroid dose and side effects
- Improved symptoms and quality of life
- ? Remission / Disease modification to prevent asthma over long term

What DON'T we achieve with biologics?

- ELIMINATION of exacerbations
- ELIMINATION of steroids
- COMPLETE IMPROVEMENT of symptoms and quality of life
- REMISSION
- DISEASE MODIFCATION to prevent asthma over long term

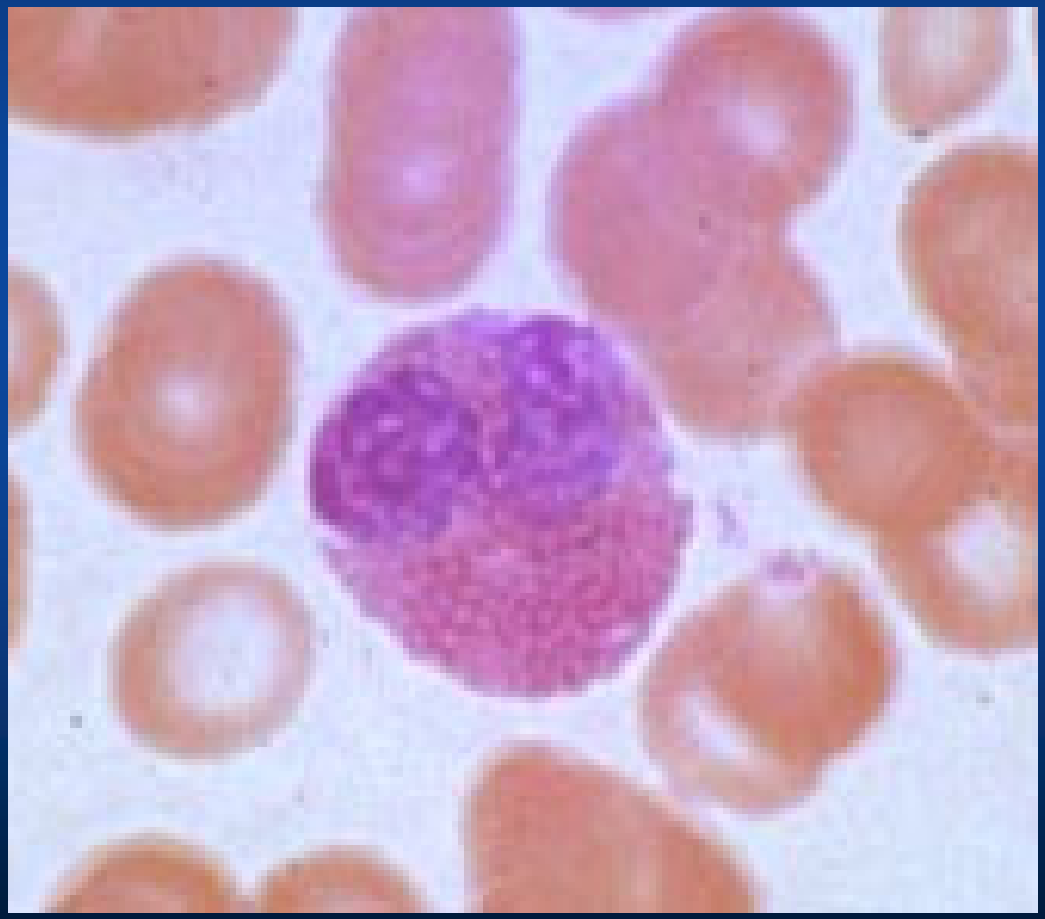
Biologics in Severe Asthma

Is the glass half full or half empty?

Severe Asthma

- Exacerbations are ONLY reduced by 50%
- Steroid dosing is ONLY reduced by 50%
- Most patients FAIL to achieve normal lung function

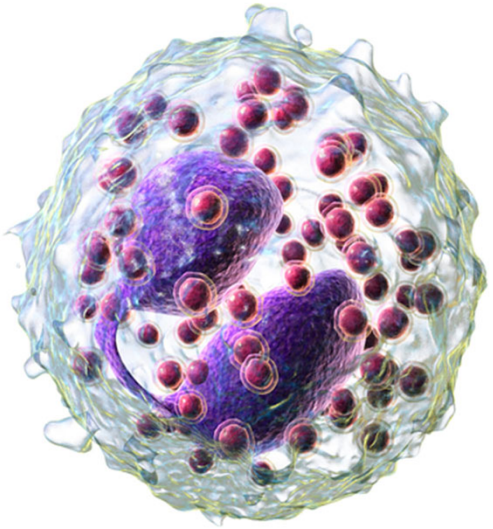
BLOCKING EOSINOPHILS WITH ANTI IL5

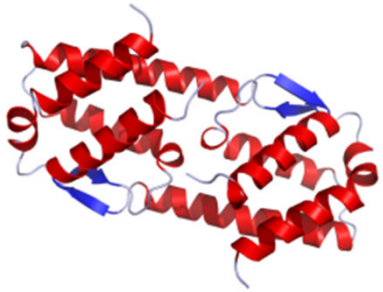


The targets: IL-5 or eosinophils (IL-5Rα)

Benralizumab

Mepolizumab
Reslizumab



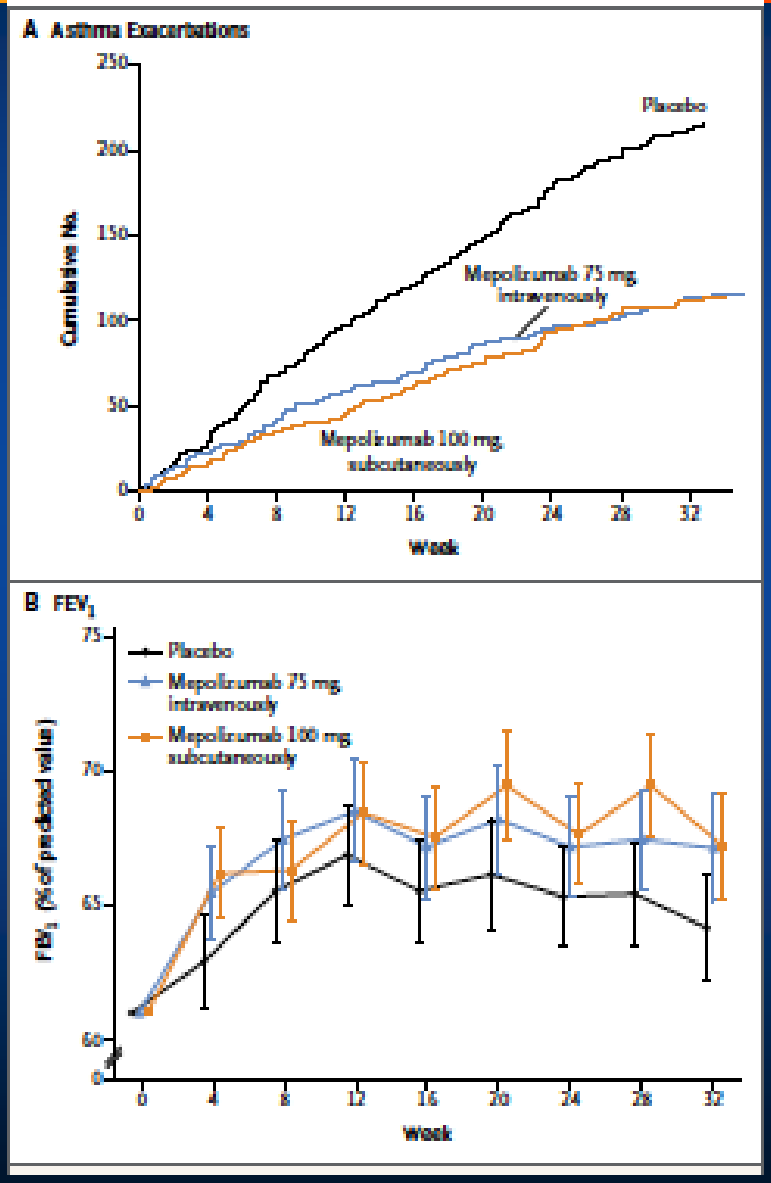


Eosinophil

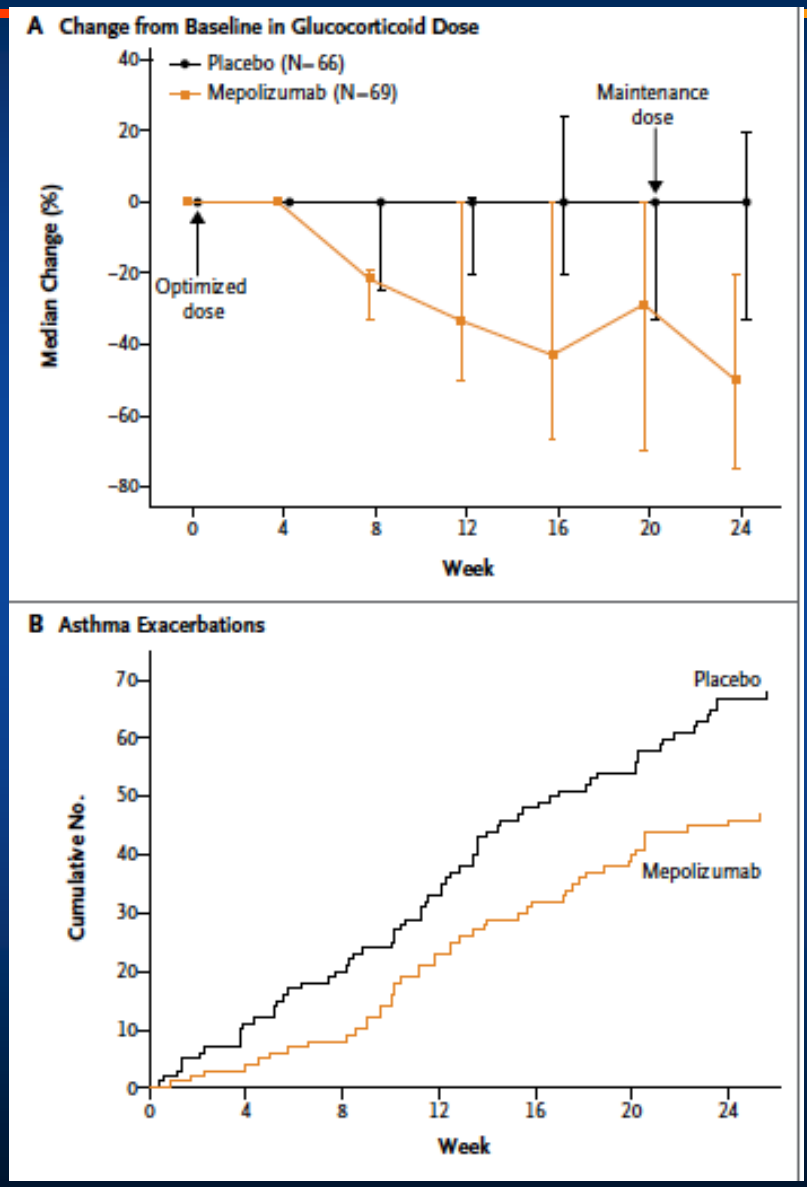
IL-5

IL, interleukin

MEPOLIZUMAB NEJM 2014

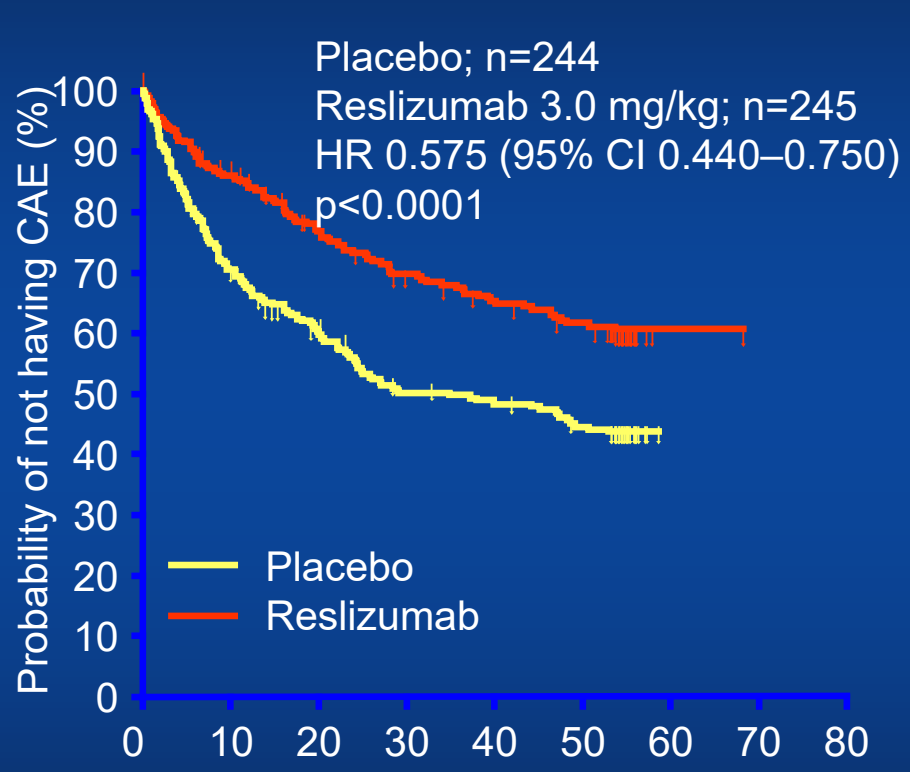


ORTEGA NEJM 2014



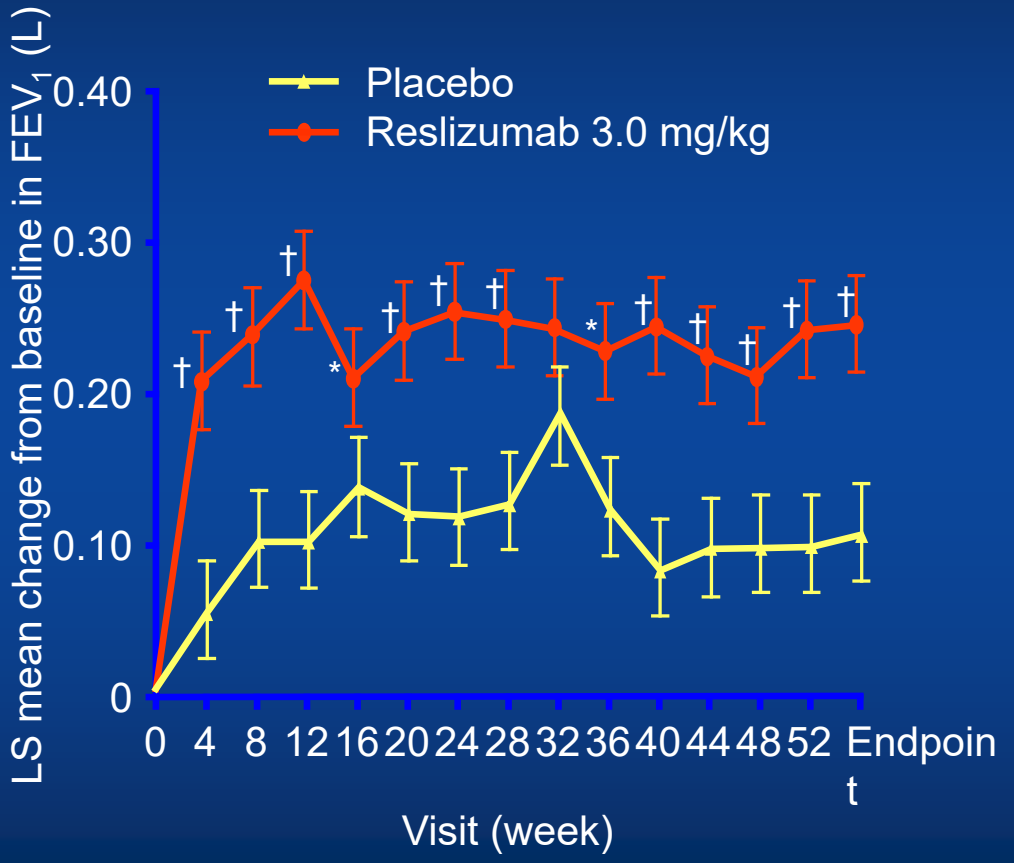
BEL NEJM 2014

Reslizumab Effects on Exacerbations and Lung Function



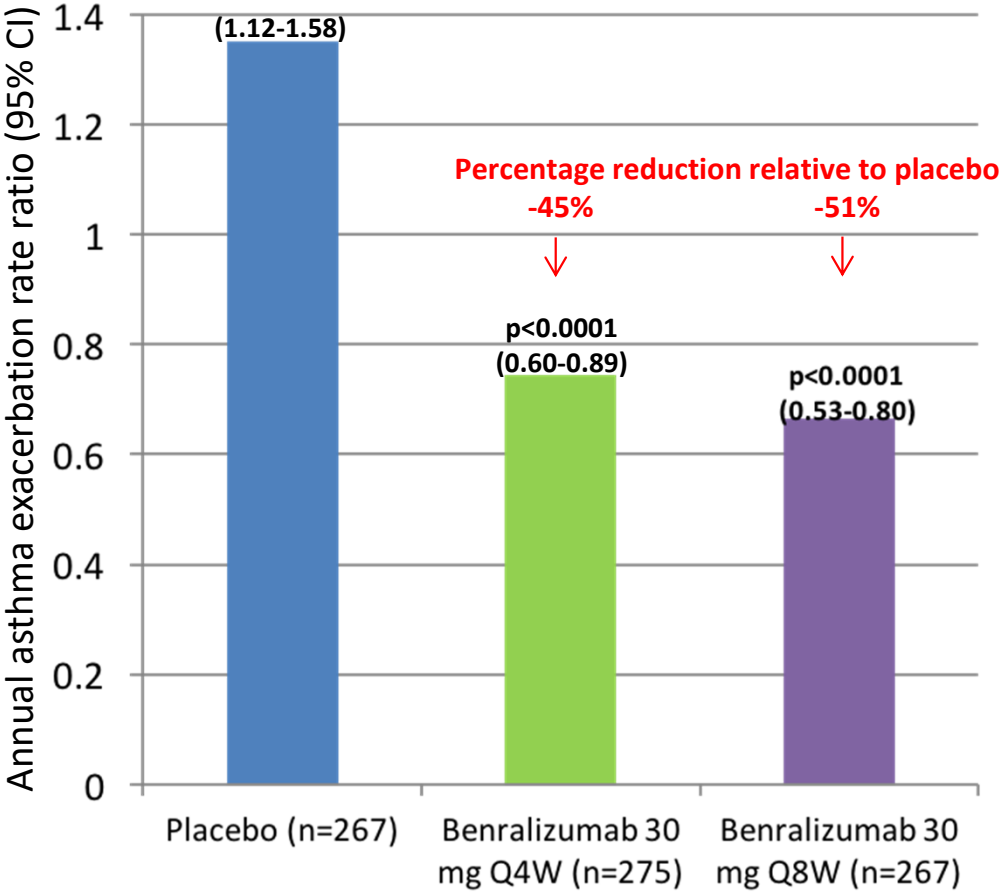
Number at risk

Placebo	244	169	138	112	107	97	0	0	0
Reslizumab	245	207	177	158	146	136	1	0	0

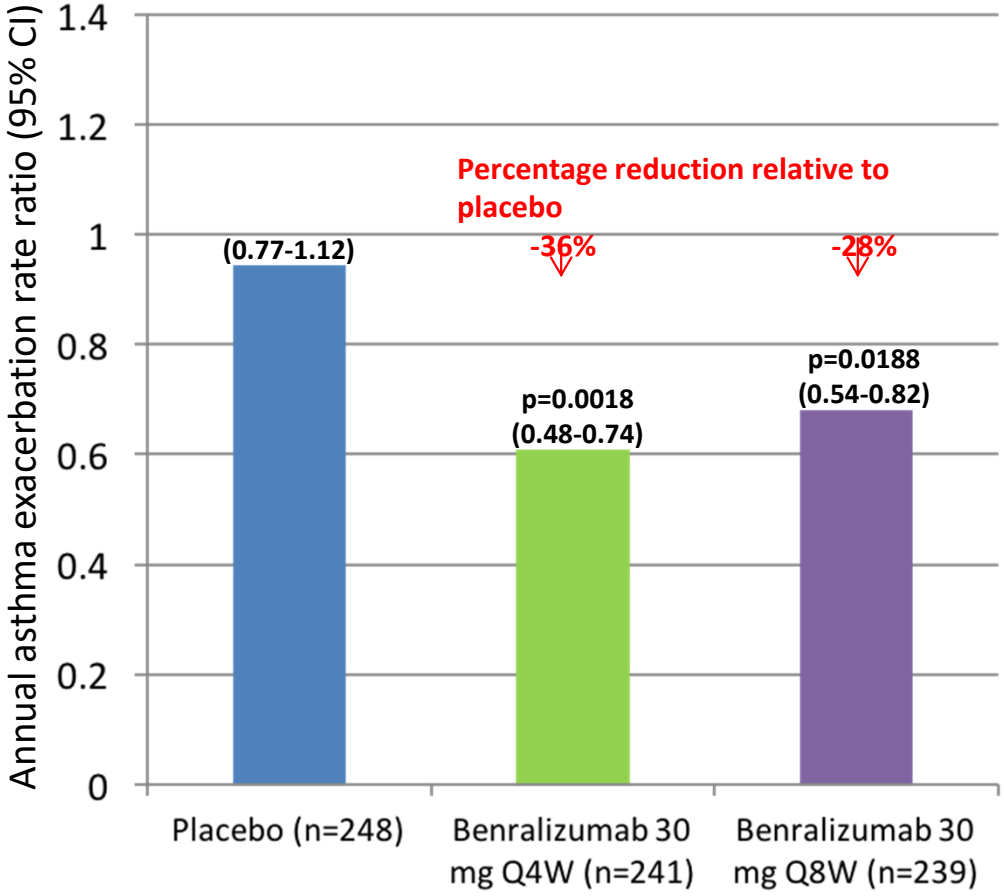


Benralizumab Reduces Exacerbation

Eosinophils ≥300 cells per µL



Bleecker ER, et al.



FitzGerald JM, et al.

Bleecker E et al. *Lancet Online Publishing, thelancet.com*. September 2016.

FitzGerald J et al. *Lancet Online Publishing, thelancet.com*. September 2016.

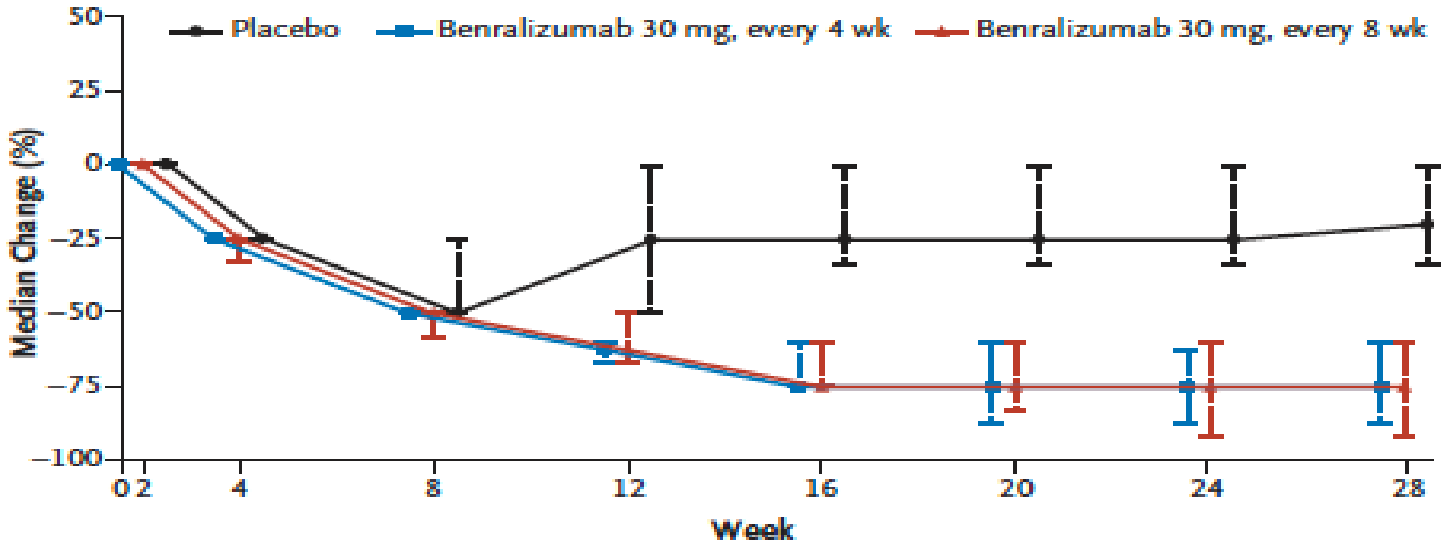
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

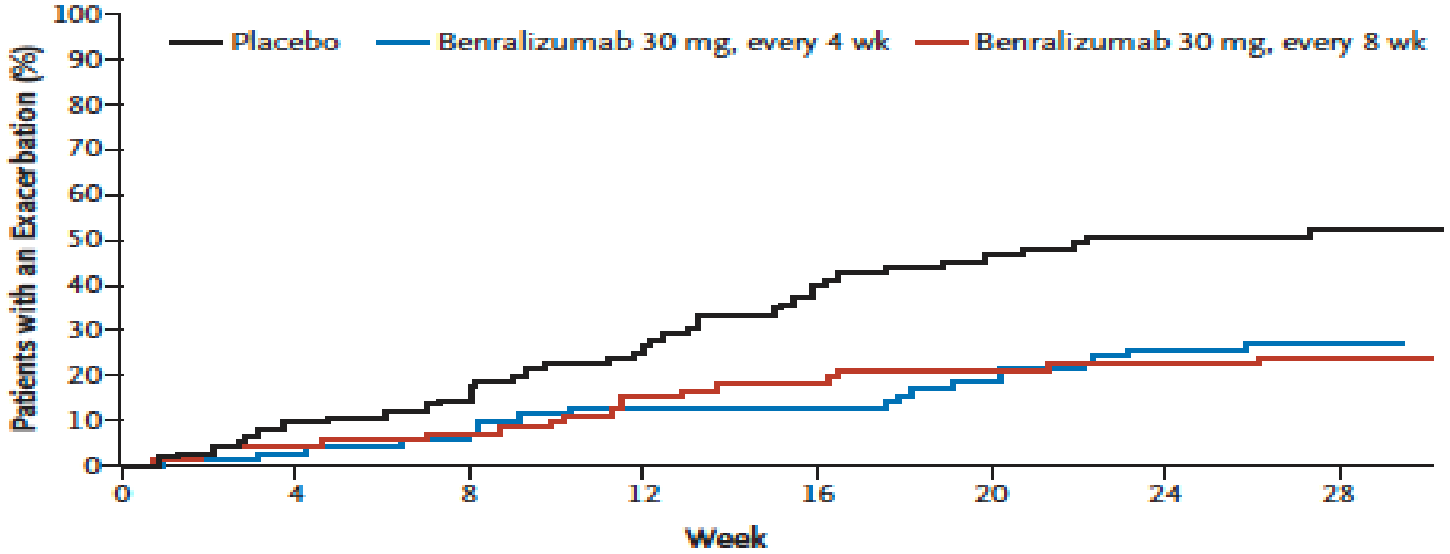
P NAIR ET AL,
NEJM MAY 2017

A Change from Baseline in Oral Glucocorticoid Dose



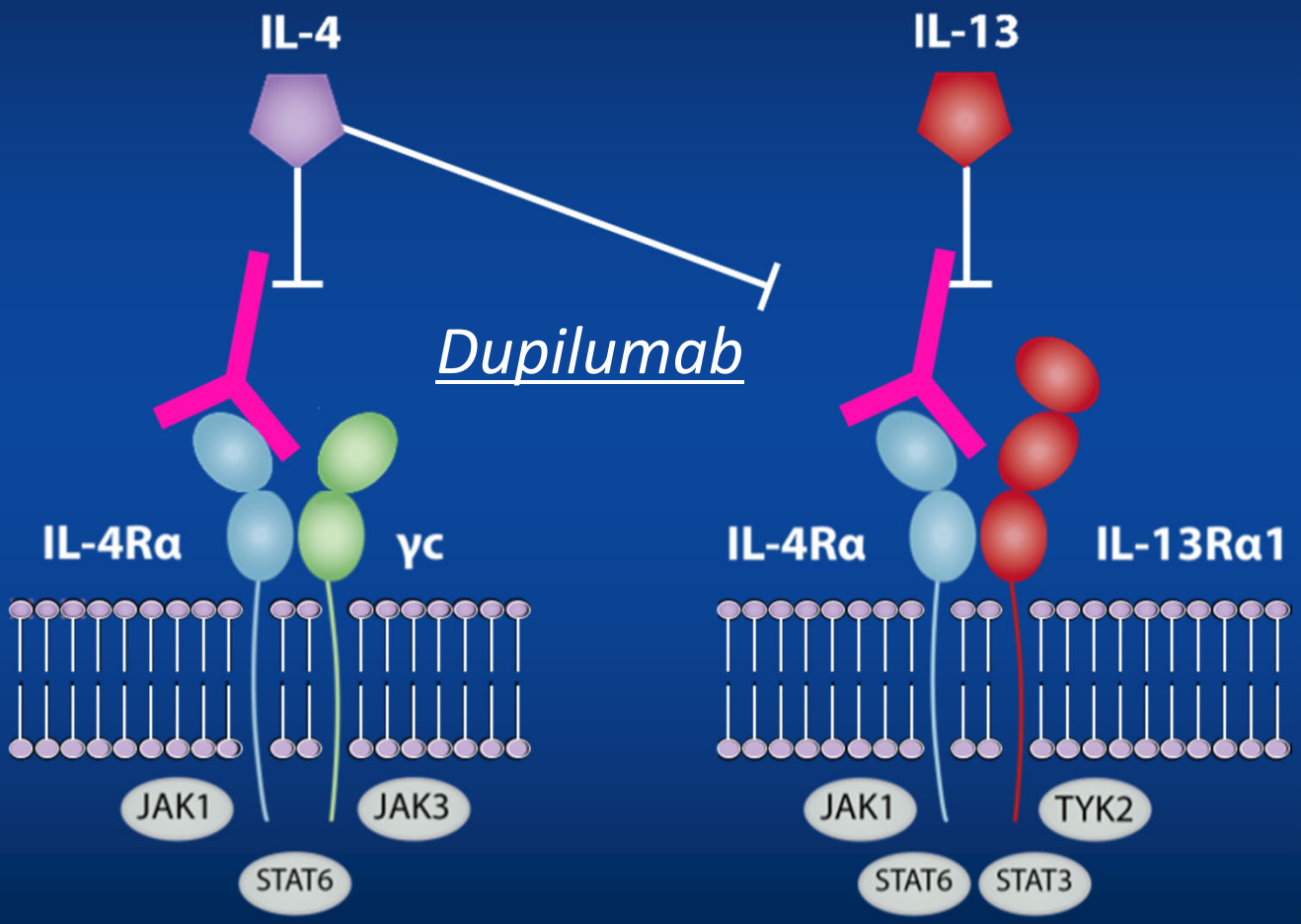
No. at Risk								
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

B Time to First Asthma Exacerbation



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

Does Broader Blockade of Type 2 Cytokines Improve Outcomes?



Anti IL4/13 and Asthma

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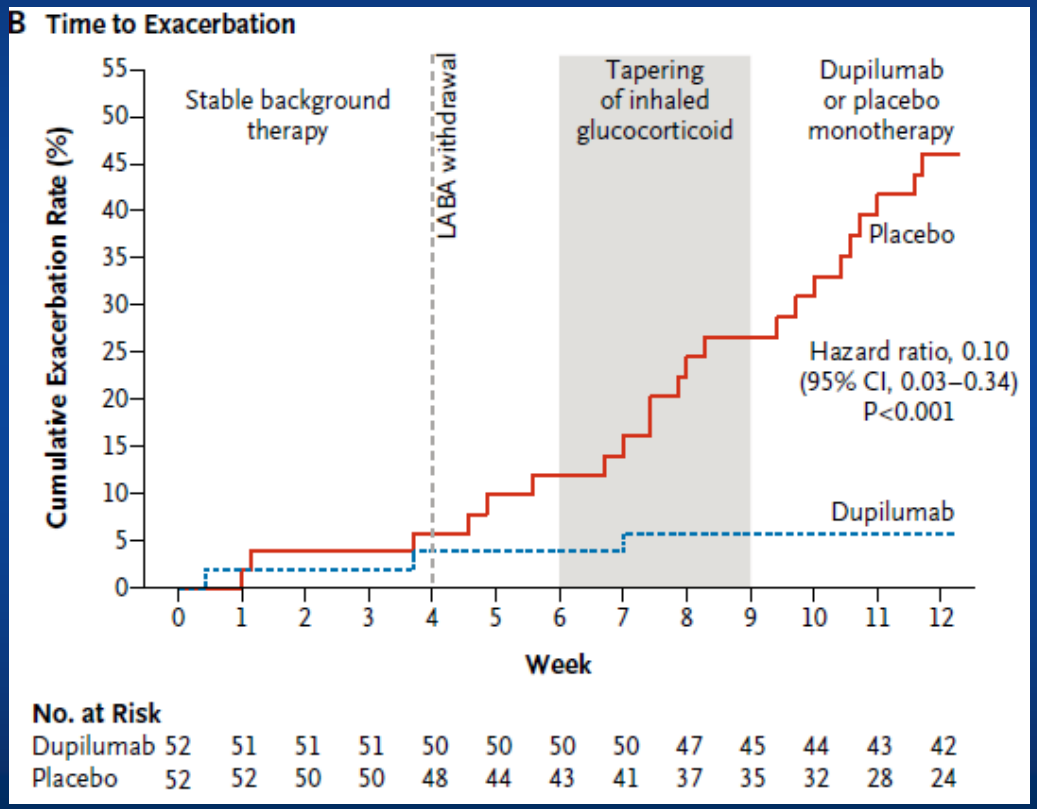
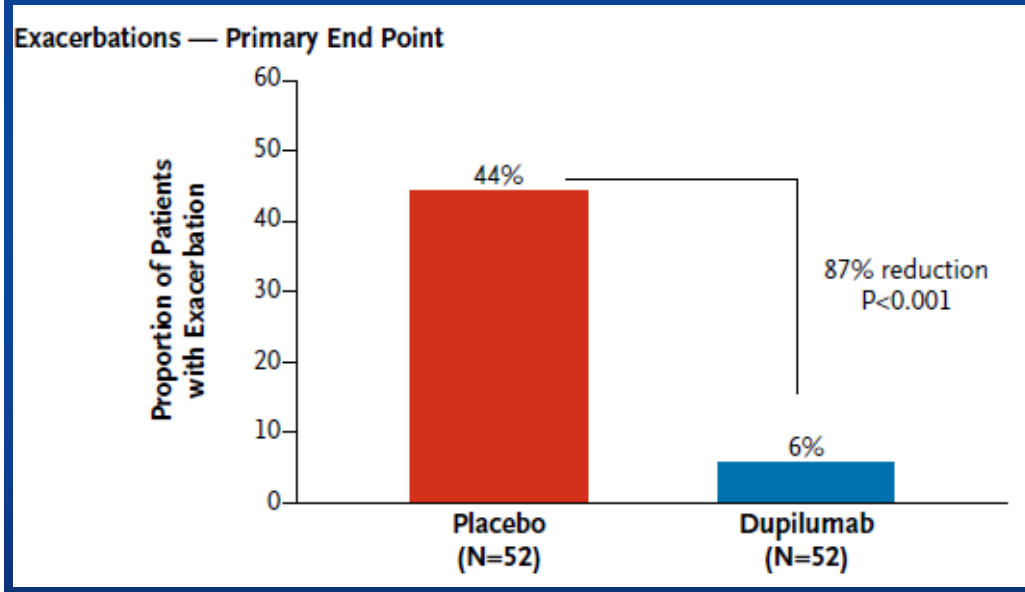
ORIGINAL ARTICLE

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

Dupilumab in Asthma





Improvement in Lung Function, On Top of Combination Rx

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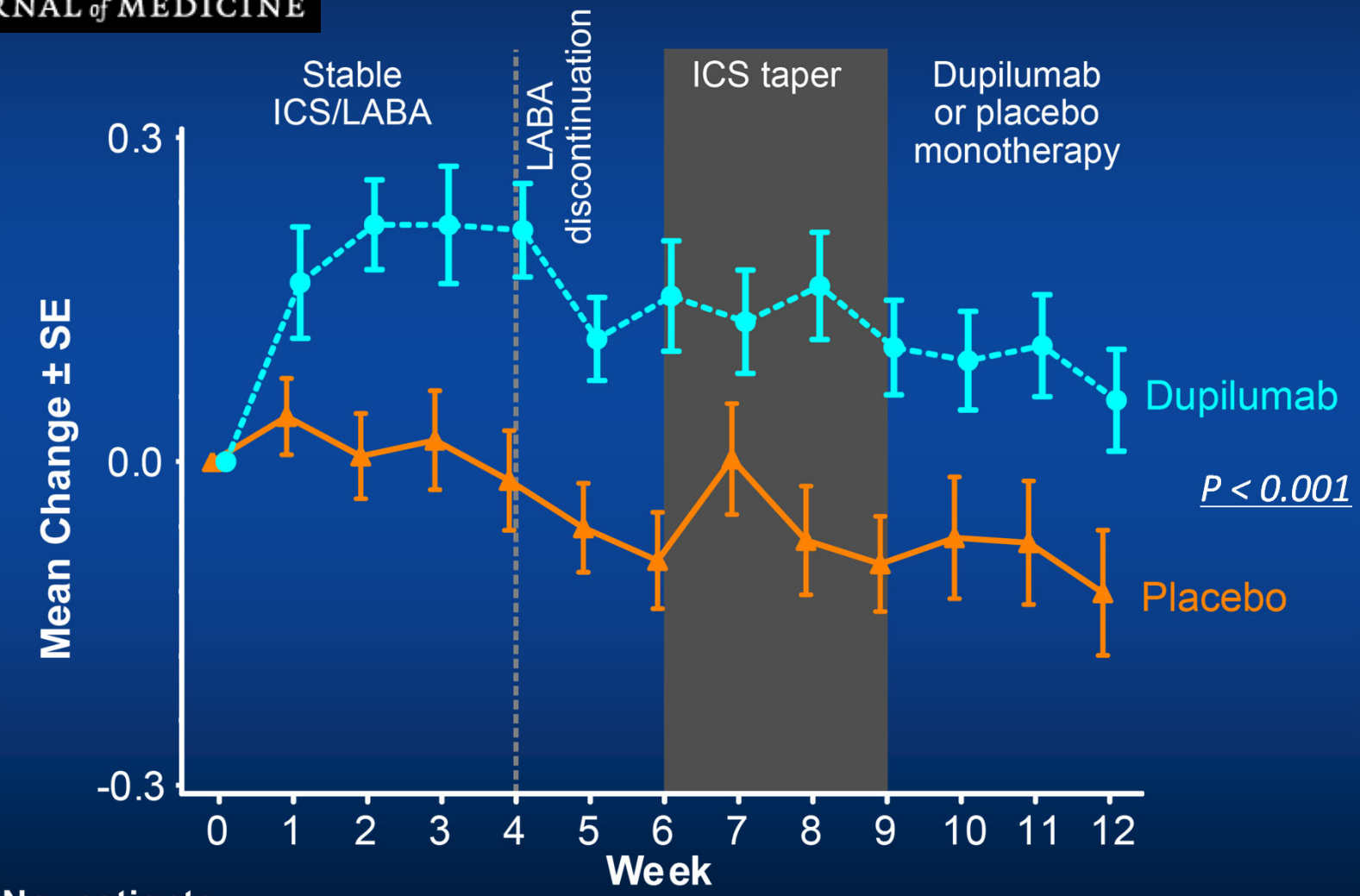


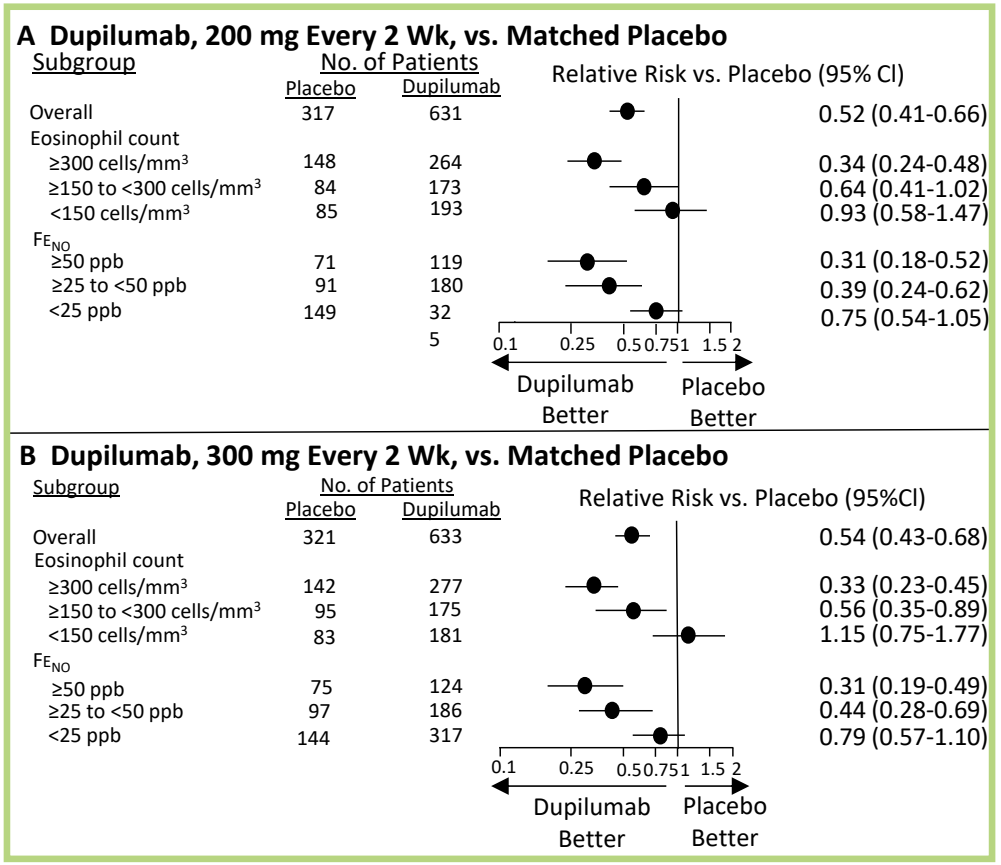
No. patients

Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45

Dupilumab Significantly Lowers Rates of Severe Exacerbation in a Phase 3 Trial

- Phase 3, randomized, double-blind, placebo-controlled trial
- n=1902 patients ≥12 years of age with uncontrolled asthma stratified by baseline blood eosinophil level
- Randomized to receive add-on SC dupilumab at a dose of 200 or 300 mg every 2 weeks or placebo for 52 weeks
- Primary outcomes: Annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in FEV_1 before bronchodilator use

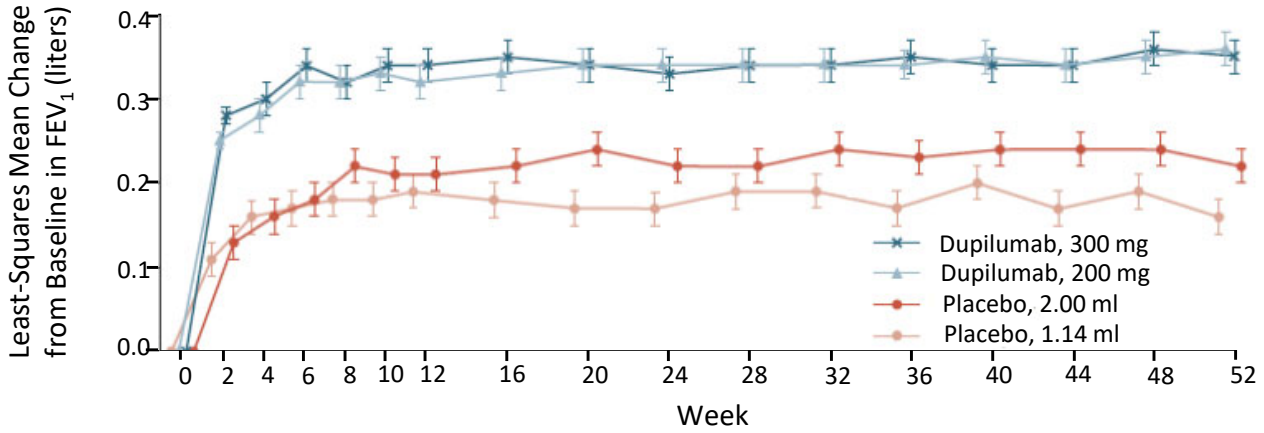
Risk of Severe Asthma Exacerbations



Castro M, Corren J, Pavord ID, et al. *N Engl J Med*. 2018;378(26):2486-2496.

Dupilumab Significantly Improved Lung Function

Change in the Prebronchodilator FEV_1 from Baseline over 52-Weeks



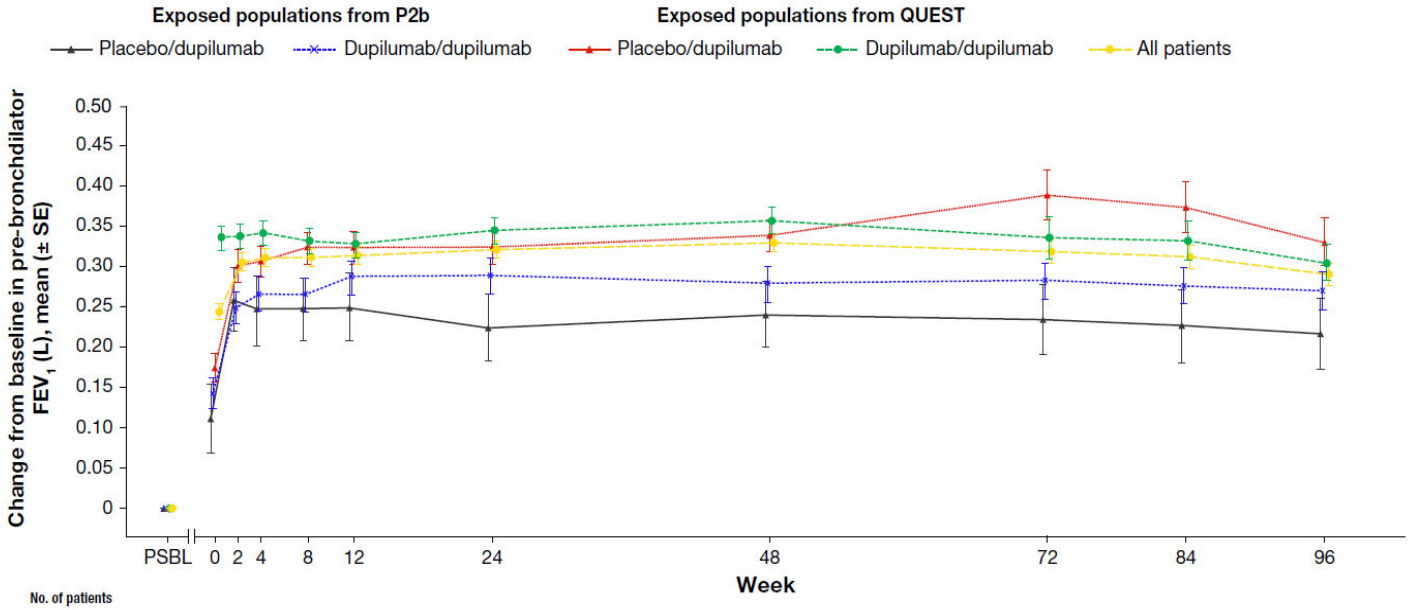
No. at Risk																	
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

The benefit of dupilumab on FEV_1 was greatest among patients with a blood eosinophil count of ≥300 eos/cc at baseline

Castro M, Corren J, Pavord ID, et al. *N Engl J Med*. 2018;378(26):2486-2496.

TRAVERSE:
LONG term benefits of 300mg Dupilumab up to 96 weeks

Improvement in FEV1 observed in the parent studies were sustained during open label treatment period



No. of patients											
Patients from P2b, placebo/dupilumab	111	111	108	111	110	110	109	105	104	102	102
Patients from P2b, dupilumab/dupilumab	421	421	412	415	410	415	409	396	383	379	380
Patients from QUEST, placebo/dupilumab	517	516	498	503	483	497	497	486	221	218	219
Patients from QUEST, dupilumab/dupilumab	1013	1010	978	980	962	972	972	951	447	444	447
All patients	2062	2058	1996	2009	1965	1999	1987	1938	1155	1143	1148

PSBL= parent study baseline

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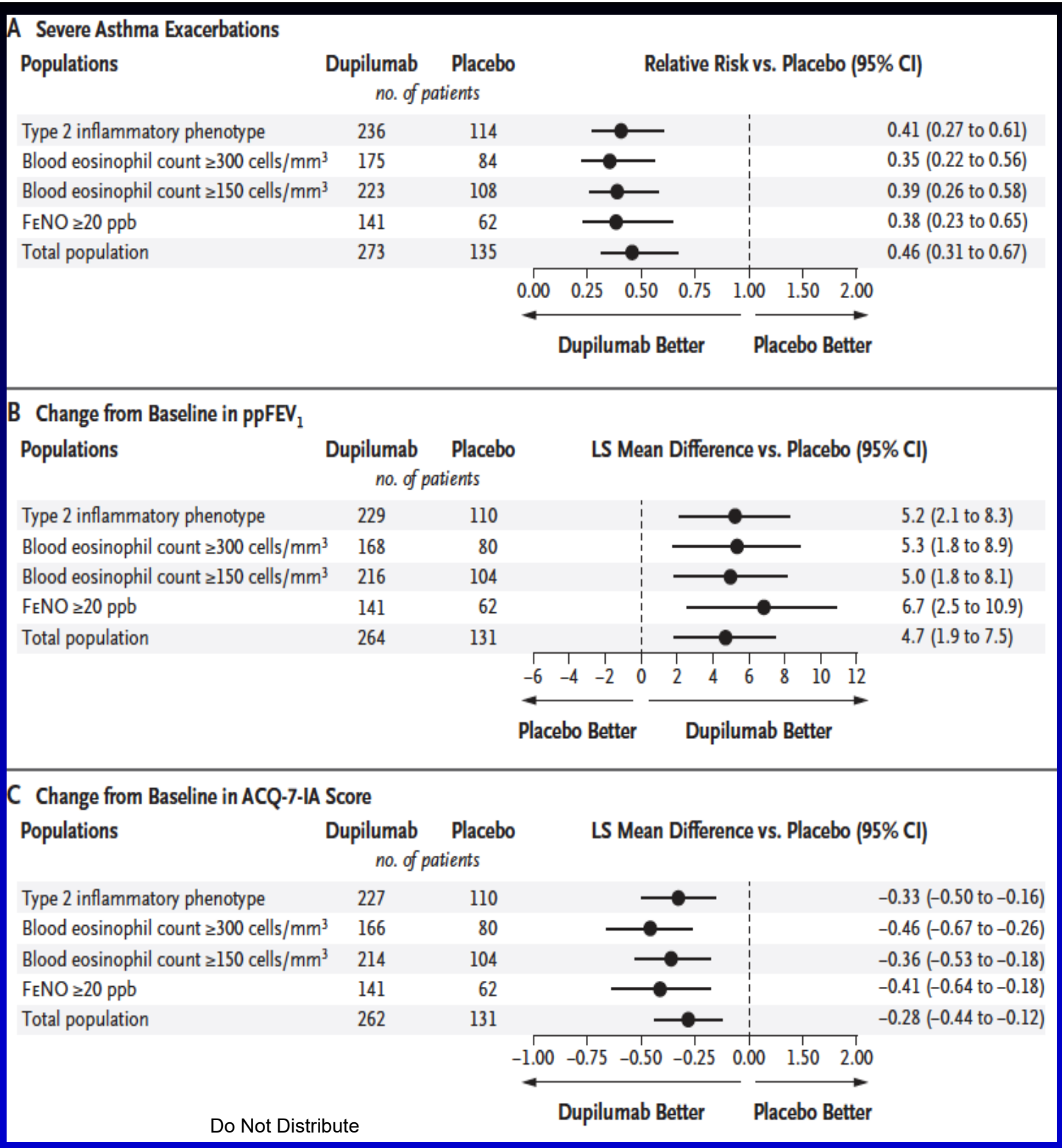
ORIGINAL ARTICLE

Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, for the Liberty Asthma VOYAGE Investigators*

Dupilumab improved outcomes in children with type 2 asthma



The NEW ENGLAND JOURNAL of MEDICINE

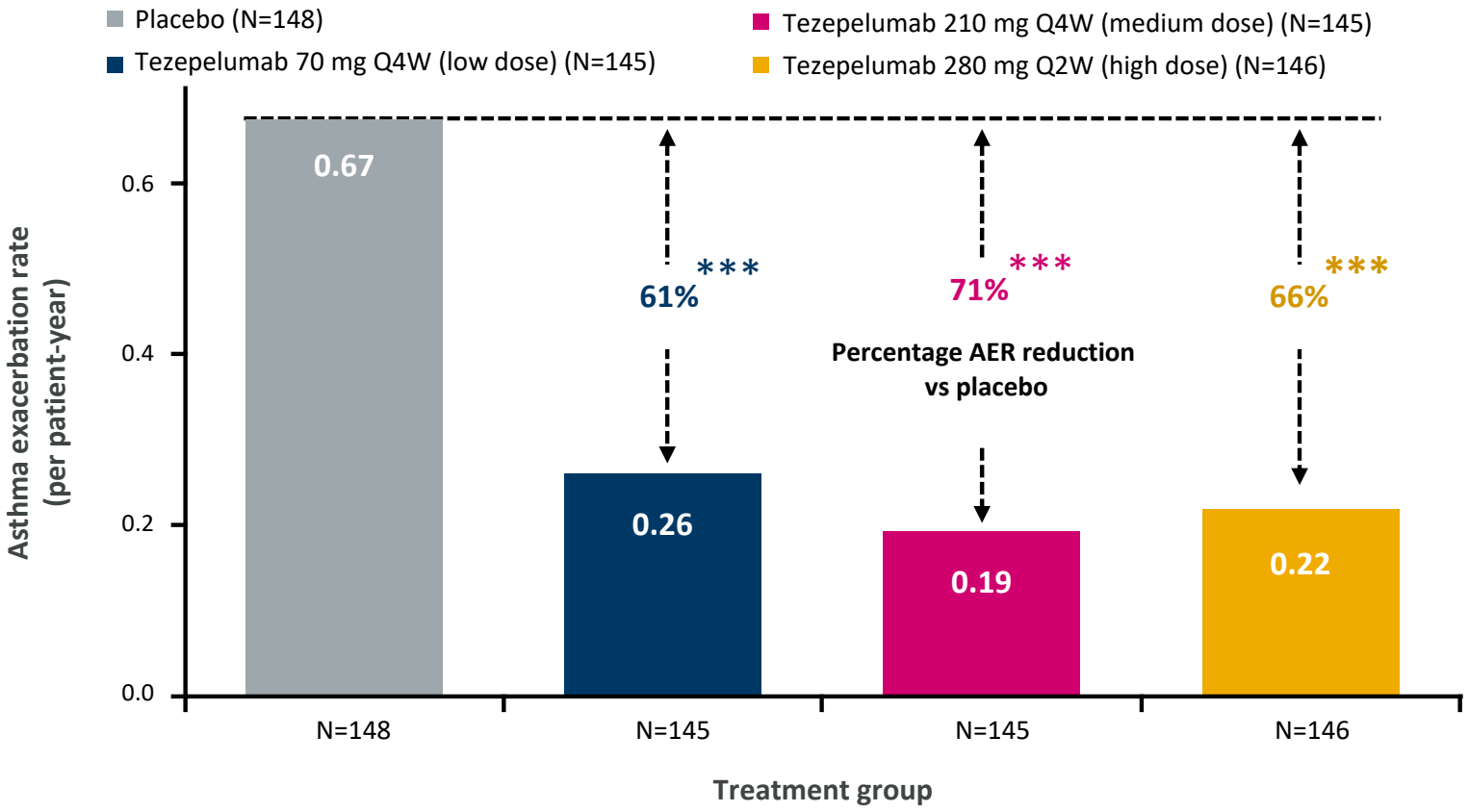
ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

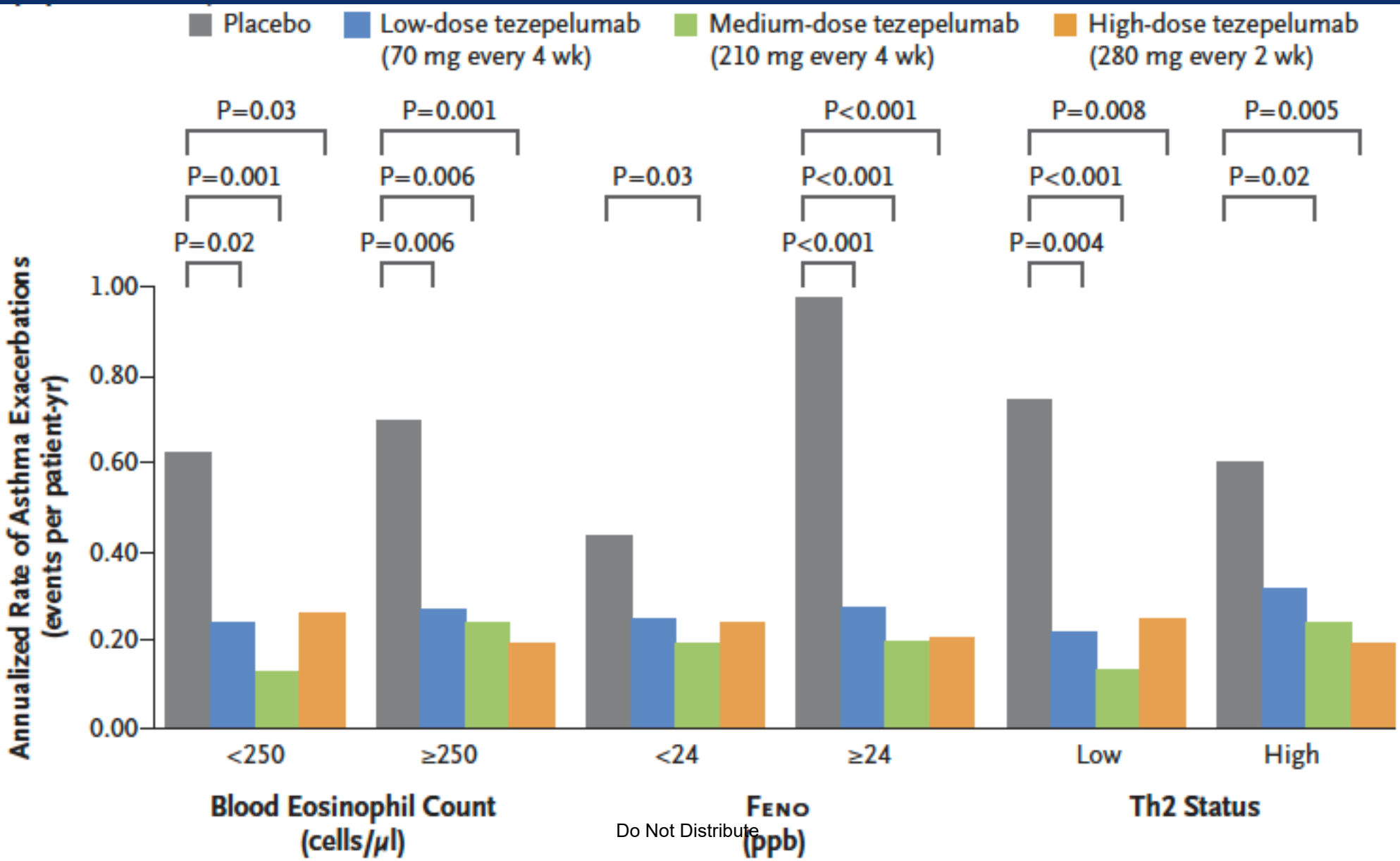
Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

Tezepelumab treatment reduced the annualised AER vs placebo at Week 52

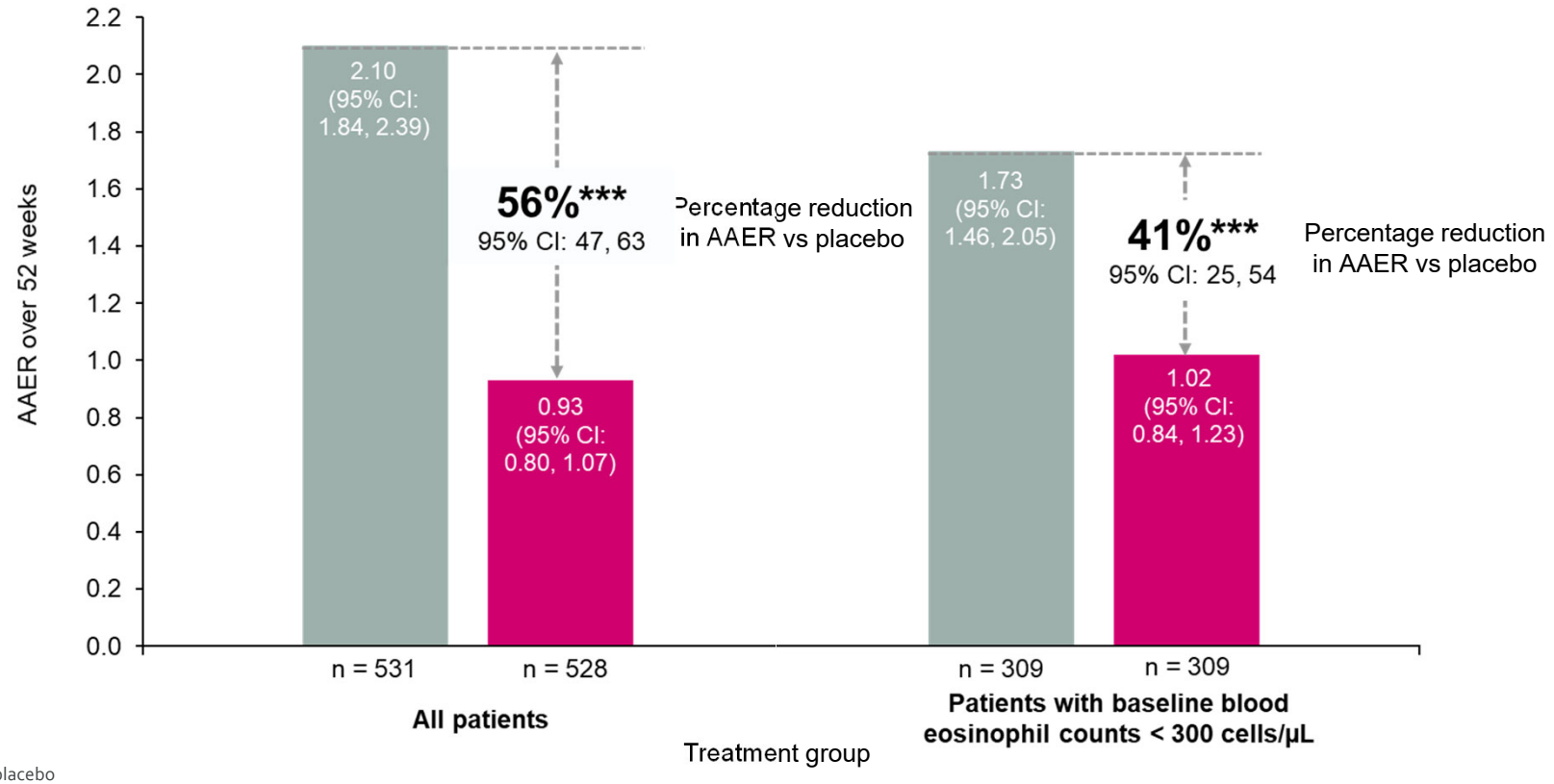
- Significant reduction in annualised AER for all tezepelumab treatment groups compared with placebo; P<0.001



Anti TSLP in Asthma (Corren 2017)



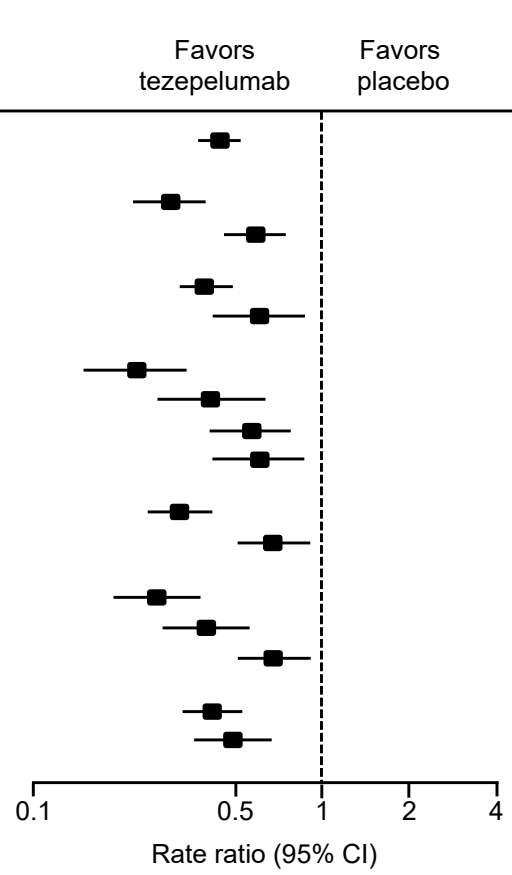
NAVIGATOR: tezepelumab reduced the annualized asthma exacerbation rate over 52 weeks (primary endpoint)



***$p < 0.001$ vs placebo
AAER, annualized asthma exacerbation rate; CI, confidence interval; Q4W, every 4 weeks

NAVIGATOR: tezepelumab reduced exacerbations in patients with a broad range of inflammatory profiles

	Tezepelumab 210 mg Q4W, n/estimate	Placebo, n/estimate	Rate ratio (95% CI)
Overall	528/0.93	531/2.10	0.44 (0.37, 0.53)
EOS at baseline (cells/μL)			
≥ 300	219/0.79	222/2.66	0.30 (0.22, 0.40)
< 300	309/1.02	309/1.73	0.59 (0.46, 0.75)
EOS at baseline (cells/μL)			
≥ 150	390/0.89	393/2.24	0.39 (0.32, 0.49)
< 150	138/1.04	138/1.70	0.61 (0.42, 0.88)
EOS at baseline (cells/μL)			
≥ 450	120/0.68	127/3.00	0.23 (0.15, 0.34)
300–< 450	99/0.92	95/2.22	0.41 (0.27, 0.64)
150–< 300	171/1.00	171/1.75	0.57 (0.41, 0.79)
< 150	138/1.04	138/1.70	0.61 (0.42, 0.88)
FeNO at baseline (ppb)			
≥ 25	309/0.82	307/2.52	0.32 (0.25, 0.42)
< 25	213/1.07	220/1.57	0.68 (0.51, 0.92)
FeNO at baseline (ppb)			
≥ 50	151/0.75	156/2.83	0.27 (0.19, 0.38)
25–< 50	158/0.87	151/2.20	0.40 (0.28, 0.56)
< 25	213/1.07	220/1.56	0.68 (0.51, 0.92)
Baseline perennial-specific IgE status (FEIA)			
Any positive	339/0.85	341/2.03	0.42 (0.33, 0.53)
All negative	184/1.09	177/2.21	0.49 (0.36, 0.67)

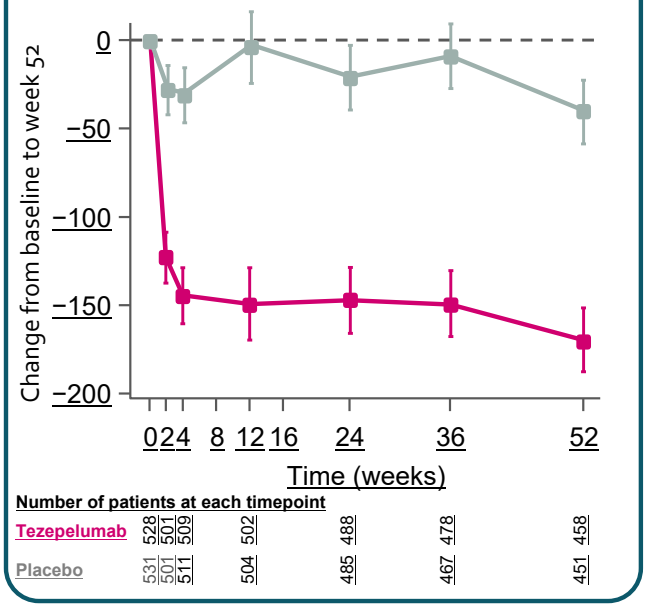


AAER, annualized asthma exacerbation rate; CI, confidence interval; EOS, blood eosinophils; FEIA, fluorescence enzyme immunoassay; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ppb, parts per billion; Q4W, every 4 weeks

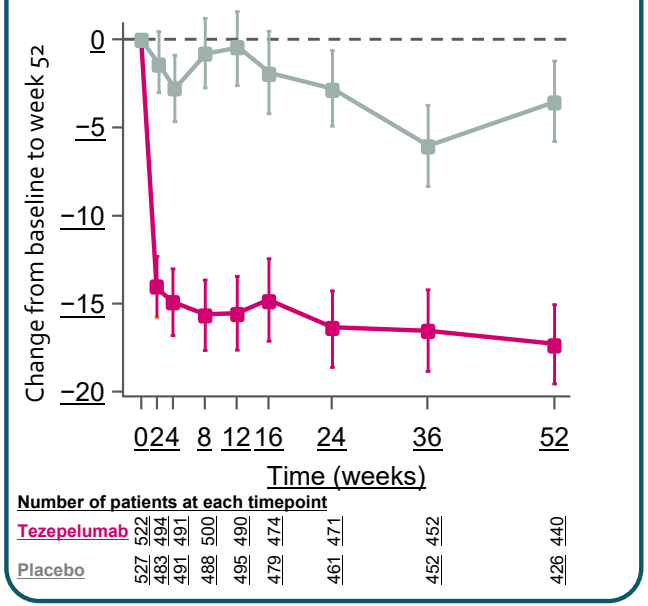
NAVIGATOR: tezepelumab reduced Type 2 Biomarkers

Placebo Tezepelumab 210 mg Q4W

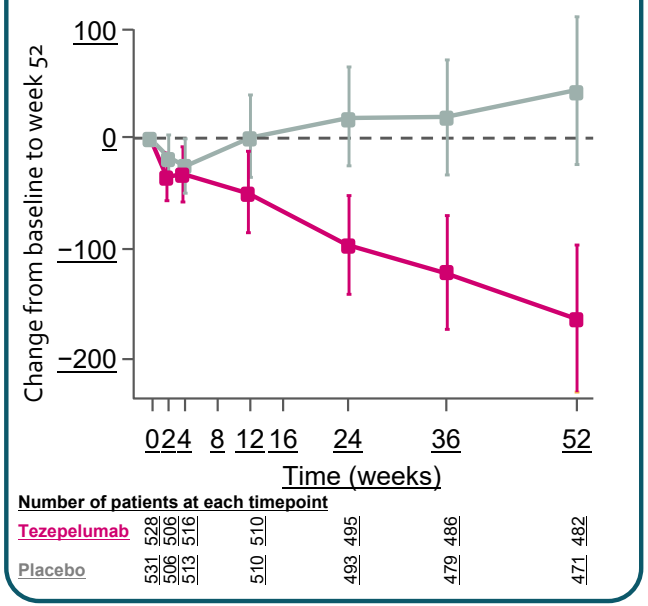
Blood eosinophil count (cells/µL)



FeNO level (ppb)



Serum total IgE level (IU/mL)



Data are LS means and 95% CIs
CI, confidence interval; FeNO, fractional exhaled nitric oxide; Ig, immunoglobulin; LS, least-squares; ppb, parts per billion; Q4W, every 4 weeks

AntiTSLP and OCS: SOURCE

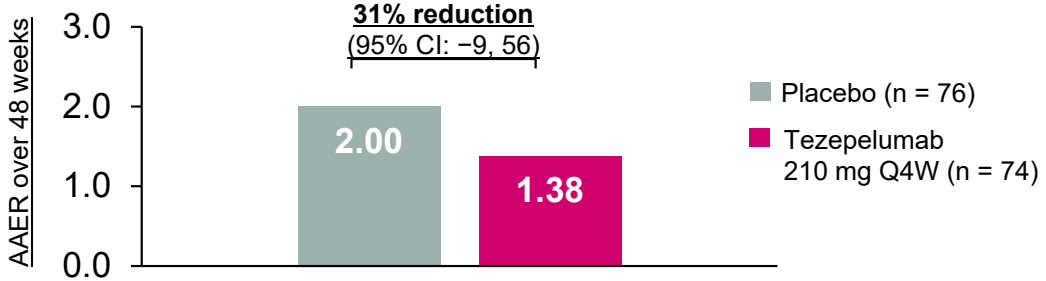
Outcome measure		Tezepelumab 210 mg Q4W (n = 74)	Placebo (n = 76)
Reduction from baseline in final daily OCS dose, n (%)	≥ 90% to 100% reduction	40 (54.1)	35 (46.1)
	≥ 75% to < 90% reduction	5 (6.8)	4 (5.3)
	≥ 50% to < 75% reduction	10 (13.5)	14 (18.4)
	> 0% to < 50% reduction	5 (6.8)	9 (11.8)
	No change or any increase	14 (18.9)	14 (18.4)
Comparison between treatment groups	Cumulative odds ratio (95% CI)	**1.28 (0.69, 2.35)**	
	p value	**0.434**	

- Lack of difference may be due in part to the large placebo effect resulting from the long duration of the OCS reduction phase and multiple attempts to reduce OCS dose
- A greater reduction in OCS dose was seen with tezepelumab versus placebo in patients with baseline EOS ≥ 150 cells/μL and ≥ 300 cells/μL. Point estimates in the < 150 and < 300 cells/μL subgroups favored placebo

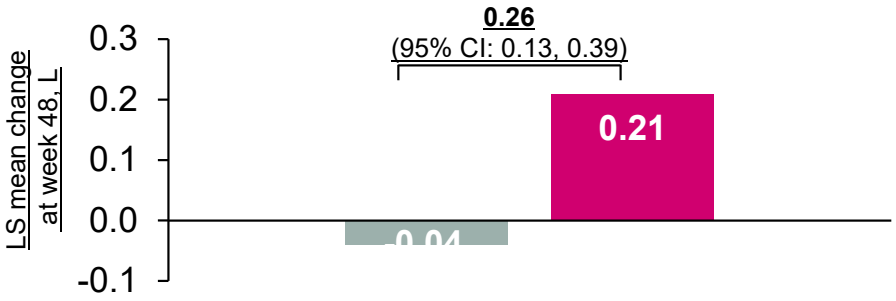
CI, confidenc

SOURCE: secondary endpoints

AAER over 48 weeks



Pre-BD FEV_1



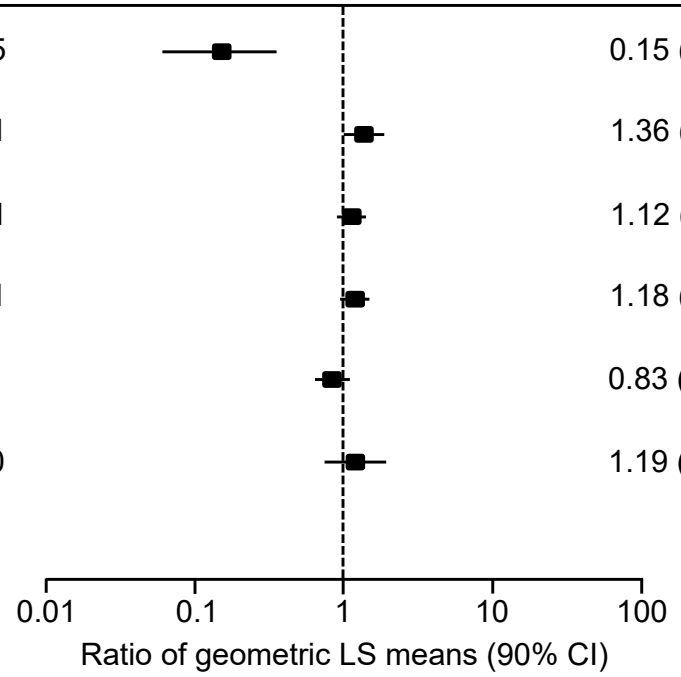
At week 48, improvements were greater with tezepelumab than with placebo for:

- ACQ-6 score: −0.87 vs −0.51; **LS mean difference, −0.37 (95% CI: −0.71, −0.02)**
- AQLQ(S)+12 overall score: 0.94 vs 0.58; **LS mean difference, 0.36 (95% CI: 0.01,**
- Asthma Symptom Diary score: −0.36 vs −0.26; **LS mean difference, −0.10 (95% CI**

AAER, annualized asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire – 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for patients 12 years and older; BD, bronchodilator; CI, confidence interval, FEV_1, forced expiratory volume in 1 second; LS, least-squares; Q4W, every 4 weeks

CASCADE: change from baseline in airway submucosal inflammatory cells in bronchoscopic biopsies (primary endpoint)

	Tezepelumab 210 mg Q4W, n/geometric LS mean	Placebo, n/geometric LS mean	Ratio of geometric LS means (90% CI)
Eosinophils (cells/mm^2)	48/0.11	51/0.75	0.15 (0.06, 0.35)
Neutrophils (cells/mm^2)	48/1.11	51/0.81	1.36 (0.99, 1.86)
T cells – CD3$^+$ (cells/mm^2)	48/0.91	51/0.81	1.12 (0.90, 1.40)
T cells – CD4$^+$ (cells/mm^2)	48/0.96	51/0.81	1.18 (0.94, 1.48)
Mast cells tryptase$^+$ (cells/mm^2)	48/0.84	51/1.01	0.83 (0.64, 1.09)
Mast cells chymase$^+$ (cells/mm^2)	48/1.07	51/0.90	1.19 (0.74, 1.92)



Analyses were performed using an ANCOVA model with log-transformed data
ANCOVA, analysis of covariance; CD, cluster of differentiation; CI, confidence interval; LS, least-squares; Q4W, every 4 weeks

Tezepelumab reduced the AAER over 104 weeks versus placebo, including exacerbations associated with hospitalization or an ED visit

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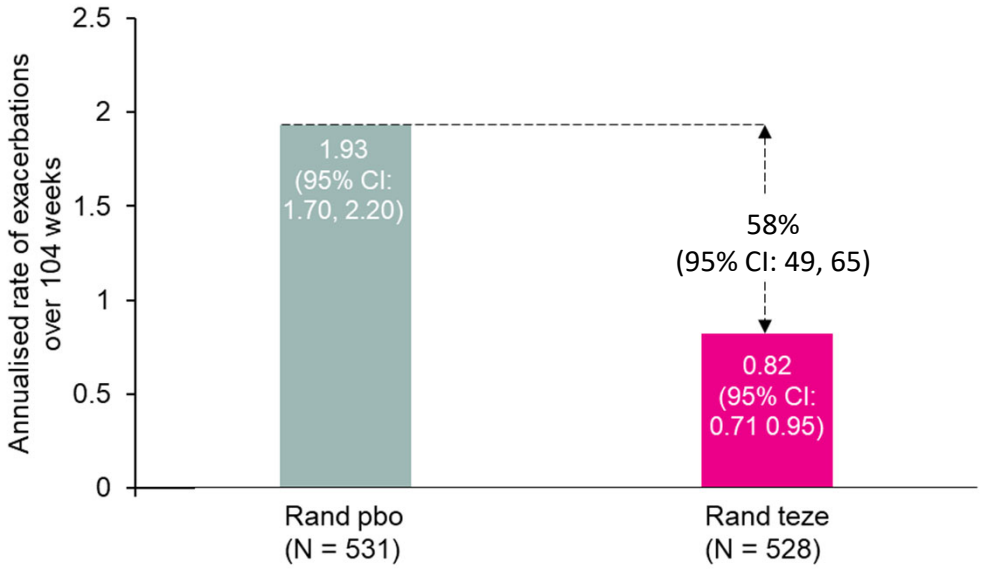
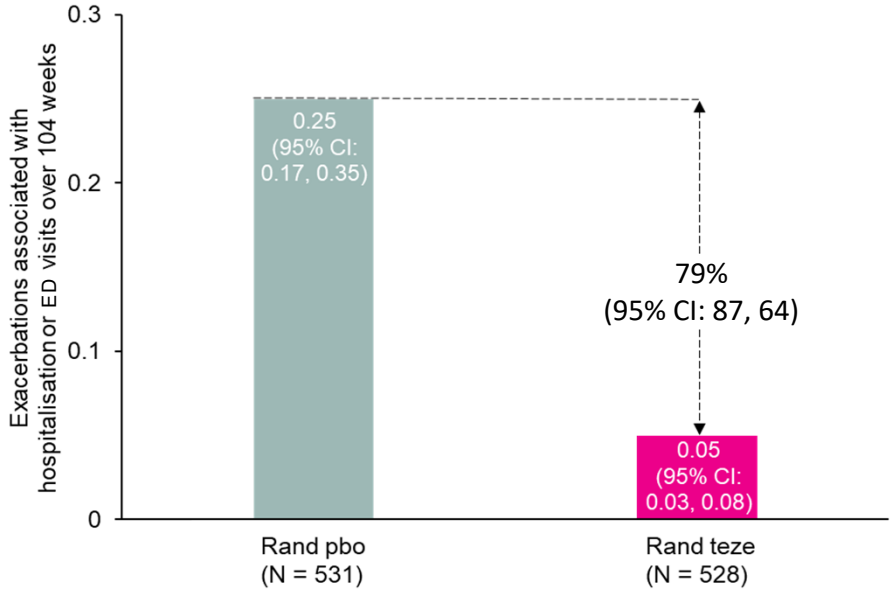
Patients initially from NAVIGATOR





AAER, annualized asthma exacerbation rate; CI, confidence interval; ED, emergency department

Targeted Biologic Approaches to Treat Asthma

	Dupilumab (SubQ)	Omalizumab (SubQ)	Benralizumab (SubQ)	Mepolizumab (SubQ)	Reslizumab (IV)	Tezepelumab (SubQ)
Target	IL-4/IL-13	IgE	IL-5 receptor	IL-5	IL-5	TSLP
Age	≥6	≥6	≥12	≥6	≥18	≥12
Frequency	q2w	q2 or 4w	q4w for first 3 doses then q8w	q4w	q4w	q4w
Other Approved Indications	Atopic dermatitis, CRSwNP	Chronic spontaneous urticarial, nasal polyps	n/a	EGPA, HES, CRSwNP	n/a	n/a
Where Approved	US, UK, Europe, other countries	US, UK, Europe, other countries	US, UK, Europe, other countries	US, UK, Europe, other countries	US, UK, Europe, other countries	US/ Canada, UK and Europe

What Can Biologics Do?

Outcomes	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Exacerbation rate reduction	25%-75	~50%	~50%	~50%	~50-70%	~50-70%
mOCS reduction		++		++	++	
Quality of life improvement		+	+	+	+	++
FEV_1 improvement	+/-	+	+/-	+	++	++

Choosing the best biologic for your patient

- Do extensive workup
- Phenotype and Endotype your patients

Asthma Biomarkers

- IGE
- FENO
- EOS
  - Sputum
  - Blood
- Periostin
- DPP4 (Dipeptidyl Peptidase 4 / CD26; an adipokine)

Factors in Choosing Biologics

- Have biomarkers been assessed?
- What is the DOMINANT biomarker?
- Are there Type 2 comorbidities?
- Shared decision making re:
  - Dosing frequency
  - Cost
- Did the patient respond to initial biologic? If no, consider switching!!!

Selecting Treatment for Severe Asthma: Anti-IgE Versus Anti–IL-5 vs. Anti IL4/13 vs Anti TSLP

Patients with allergic eosinophilic asthma → **Anti-IgE or Anti–IL-5 or Anti IL4/13 Or Anti TSLP**

Patients with allergic noneosinophilic asthma → **Anti-IgE or Anti IL4/13 or Anti TSLP**

Patients with eosinophilic asthma who:
- Are nonallergic

OR
- Do not respond to anti-IgE treatment

OR
- Are out of range of dosing for anti-IgE treatment

→ **Anti–IL-5 or Anti IL4/13 or Anti TSLP**

- Other factors influencing the decision: patient comfort with a new agent vs older treatment with more experience

Head-to-head studies are needed

1. Papathanassiou E et al. *Eur Clin Resp J*. 2016;3:31813. 2. Magnan A et al. *Allergy* 2016;71:1335-1344.

What about non type 2 asthma?

- Azithromycin
- Bronchial Thermoplasty
- Tezepelumab

Assessing Response to Asthma Biologics

- When?

Assessing Response to Asthma Biologics

- How to assess response?
  - Which outcomes?
    - Exacerbations
    - Symptoms
    - Lung function
    - ?biomarkers
  - Partial responder vs. complete/super responder
  - ?sustained response= ?remission

Proposed Elements Evaluated in Definitions of Remission[1,2]

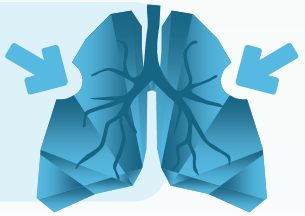
REMISSION: A state or period with low to no disease activity that can be spontaneous or as a result of biologic therapy[3]

Asthma-Related Events

Exacerbations; OCS use

FEV_1

Lung Function

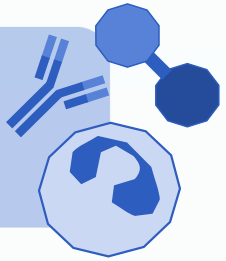


Daily Symptoms*

ACQ; ACT

FeNO; EOS; IgE

Type 2 Biomarkers



*There should be agreement between the HCP and patient regarding symptom improvement and remission.

ACQ, Asthma Control Questionnaire; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; OCS, oral corticosteroids.

1. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 2. Menzies-Gow A, et al. *Adv Ther.* 2022;39(5):2065-2084. 3. The Free Dictionary. remission. (n.d.) Collins Dictionary of Medicine. (2004, 2005). Retrieved October 6, 2022, from https://medical-dictionary.thefreedictionary.com/remission

Multiple analyses of asthma remission have been published

For ≥12 months:	Dupilumab 2021[1] QUEST Phase 3	Dupilumab 2022[2] TRAVERSE OLE	Benralizumab 2022[3] SIROCCO/CALIMA Phase 3	Benralizumab 2022[4] ANDHI Phase 3b	Mepolizumab 2022[5] REDES Real-world	Tezepelumab 2022[6] NAVIGATOR Phase 3
Absence of symptoms*† **and** 	ACQ-5 <1.5	ACQ-5 <1.5	ACQ-6 <1.5 or ≤0.75	ACQ-6 <1.5 or ≤0.75	ACT ≥20	ACQ-6 ≤0.75
Optimized/stabilized lung function **and** 	**Post-BD** FEV_1 pp ≥80%	**Post-BD** FEV_1 ≥80% OR pre-BD FEV_1 ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Not assessed	Pre-BD FEV_1 pp >80% OR Pre-BD FEV_1 >20% from BL
No exacerbations; no OCS‡ 	✓	✓	✓	✓	✓	✓§

BUT

Remission was achieved in only 8-38% of subjects depending on definition used

*Sustained absence of significant asthma symptoms based on validated instrument. †There should be agreement between the HCP and patient regarding symptom improvement and remission. ‡No use of systemic corticosteroids for exacerbations OR long-term disease control. §In this analysis, exacerbations and OCS use were individually evaluated.

ACQ-5/ACQ-6, 5-item/6-item Asthma Control Questionnaire; ACT, asthma control test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroids; OLE, open-label extension; pp, percent predicted.

1. Pavord ID, et al. Poster presented at: American College of Allergy, Asthma, and Immunology (ACAAI); November 4-8, 2021; New Orleans, LA, USA. 2. Pavord ID, et al. Poster presented at: Australian Society of Clinical Immunology and Allergy (ASCIA); August 30-September 2, 2022; Melbourne, Australia. 3. Menzies-Gow A, et al. *Adv Ther*. 2022;39(5):2065-2084. 4. Harrison T, et al. Presented at: American Thoracic Society (ATS) International Conference; May 13-18, 2022; San Francisco, CA, USA. Poster 625. 5. Domingo Ribas C, et al. Presented at: American Thoracic Society (ATS) International Conference; May 13-18, 2022; San Francisco, CA, USA. Poster 606. 6. Castro M, et al. Poster presented at: European Respiratory Society (ERS); September 4-6, 2022; Barcelona, Spain.

Summary-Current biologics

- Current biologics make a big difference
- MANY CHOICES
- Choosing best biologic can be challenging
- Need head to head trials
- Goal should be super-response/remission
- If response incomplete, consider switch!
- Many new drugs on horizon

Novel Asthma Therapies

- Anti IgE- Omalizumab
- Anti IL5: mepolizumab, reslizumab, benralizumab
- Anti IL4- R alpha/Anti IL13: dupilumab
- Anti TSLP: Tezepelumab
- Other Novel therapies:
  - Anti IL33
  - Anti IL17
  - Anti IL6
  - Dexpramipexole
  - Depemokimab Long acting Anti IL5
  - Verekitug Long acting anti TSLP
  - Jak inhibitors
  - Anti M1’
  - Anti Gata3 DNAzyme
  - TLR9 agonists
  - Antibiotics
  - FAILED: CRTH2 Antagonists- (Fevipiprant) Anti IL13 (lebrikizumab, tralokinumab)

Future Biologics Questions

- Can we give biologics to young kids to prevent asthma
- Should we give biologics to mild-moderate patients to prevent progression
- When do we stop biologics?
- Can we stop ICS/LABA in biologic patients or the biologic if well controlled
- Are there other biomarkers/pathway to target?
- Better biologics for nontype 2 disease

Thanks!!
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